INSPECTIONS AND RISK:
A Regulatory Perspective

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The Regulatory Pendulum

Centralization

Enforcement

Legal emphasis

Privatization

Process

Decentralization

Education

Science-based

Government

Content

Risk

- **Product**
  - **What can go wrong?**
  - **What is the likelihood?**
  - **What are the consequences?**
- **Process**
  - **Identification of critical processes**
  - **Identification of critical process points**
  - **Control critical process points**
- **Regulatory**

Risk analysis process

- Use research and scientific information in quantitative analyses to inform risk management strategies
- Estimates likelihood & magnitude of risk
- Evaluate and compare interventions
- Define data gaps and research needs

Uncertainty in Risk

- **Common problem in risk-benefit analyses, especially in facing acute challenges**
- **We are used to it and can use statistical methods/estimates/safety factors etc.**
- **Particularly difficult with rare events and/or non-unique outcomes/multiple pathways**

Risk Assessment Applied to Drug Quality

- Control of process steps critical to product performance
- Focus on what is important
- Requires knowledge of physical and chemical attributes that affect product performance
- Life cycle
- Facilitated by technology (chemical and engineering)

Risk Assessment Applied to the Regulation of Drug Quality

- **Regulatory oversight commensurate with risk**
  - **Approval requirements**
    - **Knowledge driven/modified**
  - **Inspectional oversight**
    - **Where we go**
    - **What we look at**
    - **Knowledge driven/modified**

Systems

- **Quality systems**
  - **Industry**
    - **Utilizes knowledge**
    - **Manages risk**
      - **Design**
      - **Feedback**
      - **Management of change**
    - **Allows regulatory decisions based on risk**
      - **Impacted by effectiveness of quality system**
      - **Assessment of ability of quality system to identify and manage risk**
    - **Continuous improvement**

Systems

- **Quality systems**
  - **FDA**
    - **Integrated review and inspection**
    - **Facilitates knowledge-based approaches and decisions**
    - **Facilitates consistency**
    - **Facilitates better guidance**
    - **Manages risk**

Systems

- **Knowledge-based systems**
  - **Identifies what is critical**
    - **Design**
    - **Feedback**
  - **Focuses efforts on control or oversight of what is critical**
  - **Orients resources**
  - **Allows risk-based decisions**
    - **Provides the science for appropriate value-based decisions**

Advanced Technology

- **Advanced analytical technology**
  - **Identification of critical product and process attributes**
    - **Often requires identification of physical and chemical parameters**
    - **Often requires the application of engineering sciences**
    - **Often requires the application of complex statistical models**

Advanced Technology

- **Advanced analytical technology**
  - **Control of critical product and process attributes**
    - **Often requires analytical technology characterized by**
      - **Ability to monitor continuously**
      - **Ability to monitor on-line**
      - **Ability to monitor on a larger scale than current methods**
      - **Ability to feedback and control on the “fly”**
      - **Ability to control physical and chemical parameters**

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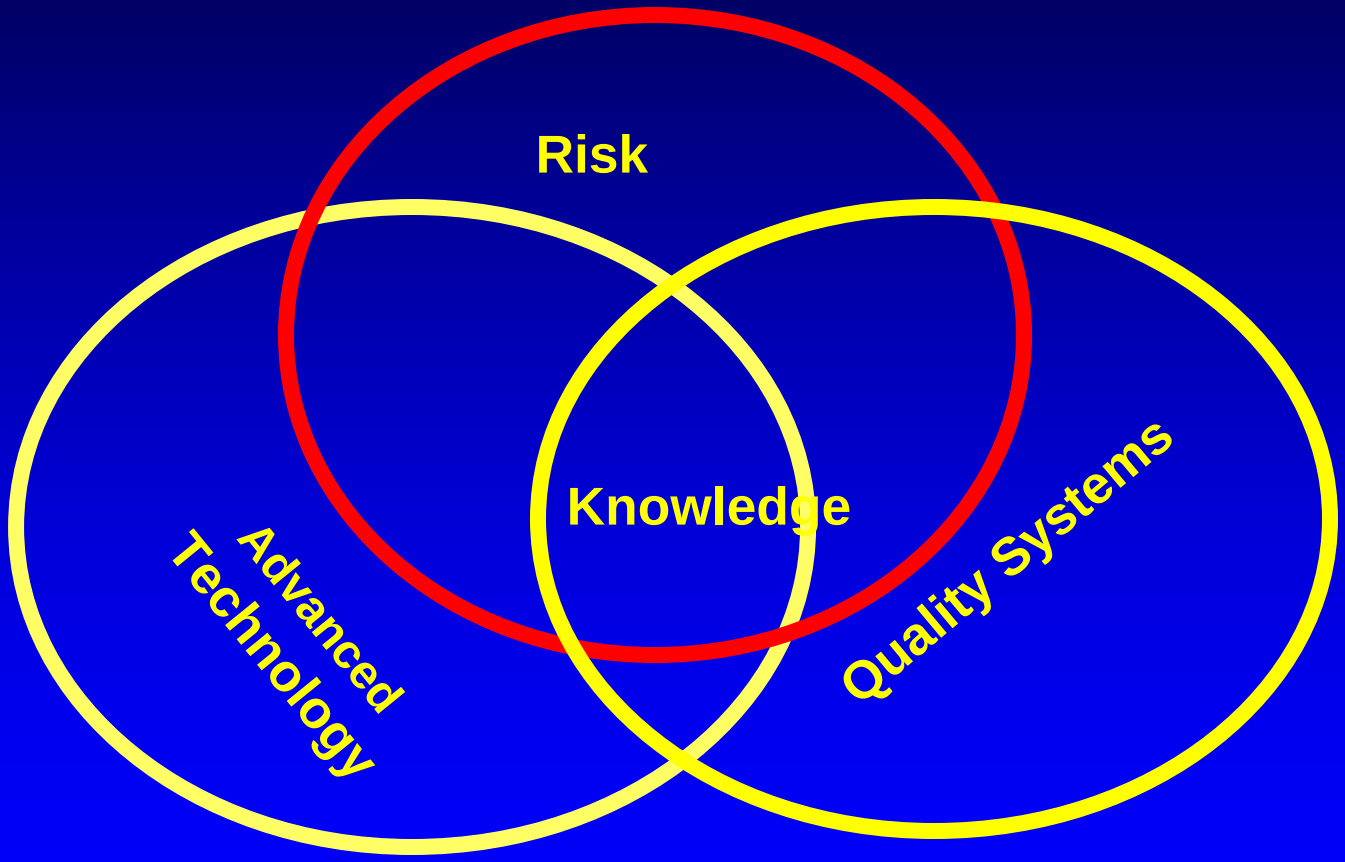
Advanced Technology

- **Advanced analytical technology**
  - **Facilitates continuous improvement**
  - **Facilitates management of risk**
  - **Allows decisions based on ability to manage risk**
  - **Focuses resources on what is critical to risk control and mitigation**
  - **Provides the science to make risk-based decisions**

The New Era



Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach

- FDA initiative announced in August 2002
- Two-year + program
- Applies to pharmaceuticals, including biological human drugs and veterinary drugs (excludes blood/plasma)
- Steering Committee comprised of CBER, CDER, CVM, CDRH*, CFSAN*, ORA, and the Office of the Commissioner

Revolution or Evolution?

A slide from a 1998 presentation

TEAM BIOLOGICS

- A plan for Reinventing FDA's Ability to Optimize Compliance of Regulated Biologics Industries
  - Joint effort of CBER and the Office of Regulatory Affairs
- Capitalize on diverse skills and knowledge
- Focus on inspectional and compliance issues

Final Report

- **Issued September 29, 2004**
- **Key accomplishments:**
  - **Quality Systems model for Agency operations**
  - **Quality Systems guidance for CGMP regulation**
  - **Adoption of risk management principles**
  - **Risk-based pharmaceutical quality assessment system**
  - **Development of science-based policies**
- **http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm**

Compliance-Related Accomplishments

- Part 11
- Dispute Resolution
- Aseptic Processing
- Comparability Protocols

"Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice"

- **Final Guidance issued September 29, 2004**
- **Recommends "building quality into products" through science-based facility, equipment, process, and system design**
  - **Ensure reliable and robust product protection through adequate design and control**
  - **Ensure that the operational and raw material inputs are predictable through adequate quality control and quality assurance**

"Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information"

- **Draft Guidance – posted September 5, 2003**
  - Guidance for use for CMC changes in approved marketing applications
  - Describes principles and procedures associated with developing and submitting comparability protocol
  - Describes consideration, development, and submission of comparability protocol and specific issues to consider for changes in manufacturing process, analytical procedures, manufacturing equipment, manufacturing facilities, container closure systems, and process analytical technology (PAT)

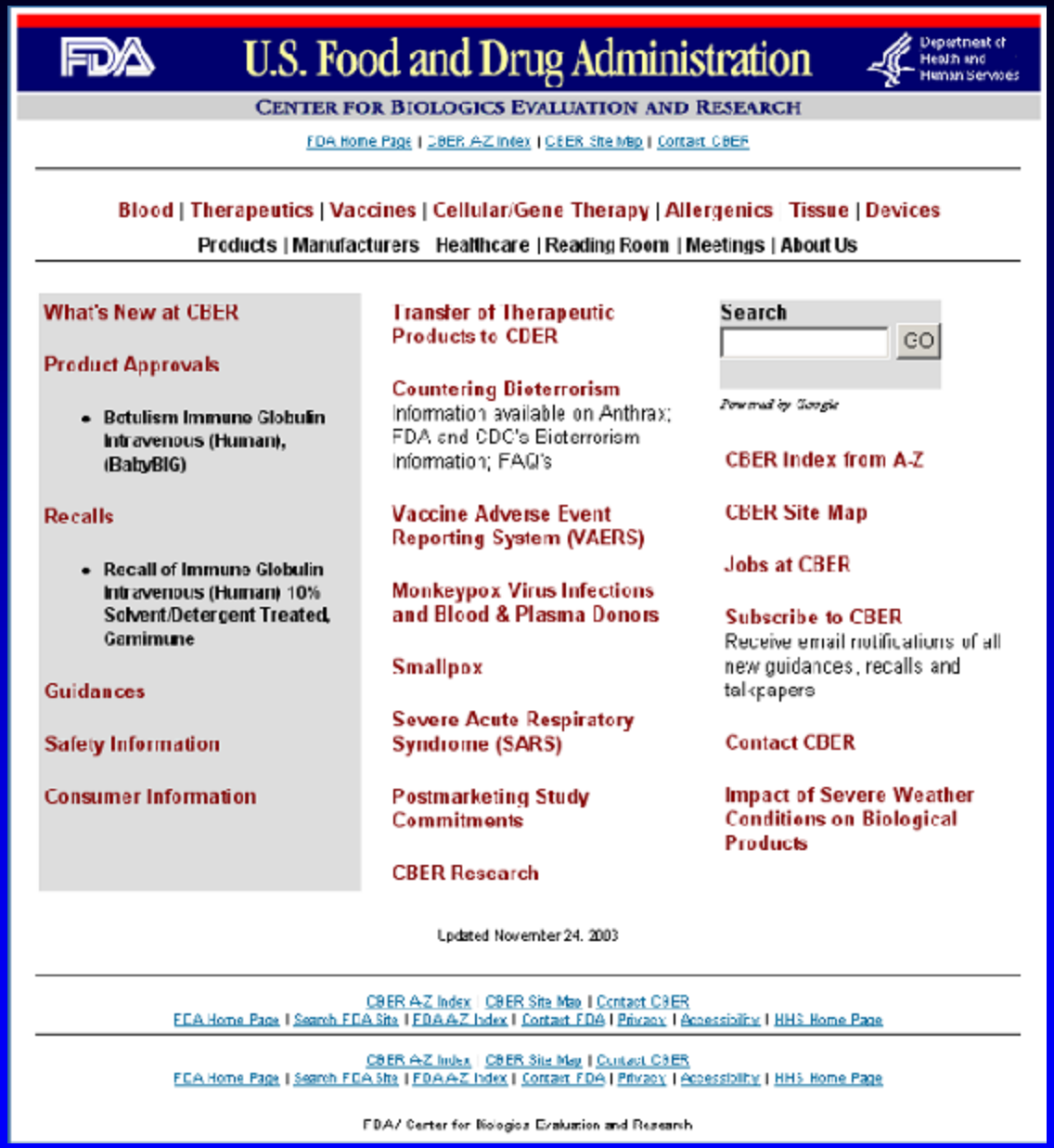
CBER

Compliance-Related Accomplishments

- **Review of Team Biologics operations**
- **Pharmaceutical Inspectorate program established by ORA and CDER on 8/22/03**
  - **Highly trained individuals**
  - **Increased use of product specialists**
  - ***Similar to existing Team Biologics and CBER biologics inspection practice (e.g., product specialists on inspections*)**

Compliance-Related Accomplishments
continued

- **Developing risk-based approach for choosing sites for inspections (CDER)**
  - ***CBER already meets statutory obligations for inspecting all licensed facilities***



U.S. Food and Drug Administration

Department of Health and Human Services

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What's New at CBER

Product Approvals

- Botulism Immune Globulin Intravenous (Human), (BabyBIG)

Recalls

- Recall of Immune Globulin Intravenous (Human) 10% Solvent/Detergent Treated, Gamimune

Guidances

Safety Information

Consumer Information

Transfer of Therapeutic Products to CDER

Countering Bioterrorism
Information available on Anthrax; FDA and CDC's Bioterrorism information; FAQ's

Vaccine Adverse Event Reporting System (VAERS)

Monkeypox Virus Infections and Blood & Plasma Donors

Smallpox

Severe Acute Respiratory Syndrome (SARS)

Postmarketing Study Commitments

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Impact of Severe Weather Conditions on Biological Products

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